In the Specification

Please replace the Title at page 1, line 1 with the following title:

C1 ANTI-CCR5 ANTIBODIES AND KITS COMPRISING SAME

Please replace the paragraph at page 1, lines 3-7 with the following paragraph:

C2 This application is a continuation-in-part application of U.S. application Serial No. 08/893,911, filed July 11, 1997 (now issued as U.S. Patent 6,528,625), which is a continuation-in-part application of U.S. application Serial No. 08/739,507, filed October 28, 1996 (now abandoned). The teachings of these prior applications are incorporated herein by reference in their entirety.

Please also replace the title on the Abstract page, at page 80, line 1, with the following title:

C3 ANTI-CCR5 ANTIBODIES AND KITS COMPRISING SAME

Amendments to the specification are indicated in the attached "Marked Up Version of Amendments" (page i).

REMARKS

Claim Numbering

Applicants thank the Examiner for noting the oversight in claim numbering in the second Preliminary Amendment filed at the United States Patent and Trademark Office on October 15, 2002, and correcting same.

Information Disclosure Statement

For the Examiner's convenience, copies of references AM, AR-AT, AU, AX, AY, AS2, AS3, AV3-AZ3, AR4 and AS5, which were temporarily unavailable for earlier consideration, are enclosed with this Amendment. Applicants respectfully request that a completely initialed copy of form PTO-1449 be returned with the next communication.

Title

The Examiner states that the Title of the invention is not descriptive and requires a new Title that is clearly indicative of the invention to which the claims are directed. Applicants have corrected the Title as required by the Examiner.

Priority

Applicants have amended the Specification to indicate the status of each parent application, as requested by the Examiner.

Rejection of Claims 83, 85, 95, 97, 107 and 109 Under 35 U.S.C. § 112, First Paragraph

Claims 83, 85, 95, 97, 107 and 109 are rejected by the Examiner under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the Specification in such as a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the Examiner has stated that the hybridoma deposited under ATCC Accession No. HB-12366 is not indicated in the specification as being deposited under the conditions of the Budapest Treaty. Applicants are submitting herewith a Declaration Under 37 C.F.R § 1.806 and § 1.808, along with a copy of the ATCC deposit receipt for HB-12366 and a copy of the Certificate of Ownership and Merger merging LeukoSite, Inc. into Millennium Pharmaceuticals, Inc. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 75-82, 84-94, 96-106 and 108-110 Under 35 U.S.C. § 112, First Paragraph

Claims 75-82, 84-94, 96-106 and 108-110 are rejected by the Examiner under 35 U.S.C. § 112, first paragraph. The Examiner states that the specification, while being enabling for antibodies that inhibit binding of the chemokines MIP-1α, MIP-1β, RANTES to human CCR5 does not reasonably provide enablement for antibodies which inhibit binding of other chemokines to any mammalian CCR5. The Examiner further states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specifically, the Examiner states that "[t]he specification appears to disclose only human CCR5, and that only the chemokines MIP-1α, MIP-1β, and RANTES bind human CCR5" (Office Action, page 4, third paragraph), and that "the skilled artisan could not reasonably predict what other chemokines would also bind CCR5." (Office Action, page 4, fourth paragraph). Furthermore, the Examiner cites Zlotnik and Yoshie (Immunity 2000; 12:121-127; IDS Ref. AZ4) to support the allegation that the skilled artisan would be required to conduct undue experimentation to identify all chemokines and test each for binding to CCR5 before these chemokines could be used to assay antibody inhibition of the chemokine binding as recited.

Applicants respectfully disagree. Zlotnik and Yoshie disclose a new classification system for chemokines. Table 1, as specifically noted by the Examiner, lists the following CCR5 ligands: MIP-1α, MIP-1β and RANTES. The Specification, as filed, listed examples of CCR5 ligands, and also included MIP-1α, MIP-1β and RANTES (see, for example, page 3, lines 2-5). Thus, Zlotnik and Yoshie do not support the Examiner's allegation that there are an unreasonable number of chemokines that bind CCR5. Indeed, it would not be undue experimentation for a person of skill in the art to identify a chemokine that binds to CCR5, instead, it is only routine experimentation that is required.

The examiner also states that "[t]he specification also does not provide sufficient guidance as to how the skilled artisan may identify, without undue experimentation, any other mammalian ortholog of human CCR5 and make and use antibodies to these other "mammalian" CCR5 proteins." (Office Action, page 4, fifth paragraph).

Applicants respectfully disagree. At the time of filing of the application, it would not be undue experimentation for one of ordinary skill in the art to identify other mammalian CCR5 proteins. The Examiner states that it would require "extensive experimentation," however the MPEP (8th ed., revision1) at § 2164.01 states that "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." (Citations omitted). At the time of filing, one of ordinary skill in the art typically researched a gene and its protein in different mammalian species and would readily appreciate how to identify a CCR5 gene and protein in different mammalian species.

Given that Applicants have provided examples of chemokines, and the level of skill in the art is such that it would not be undue experimentation to determine which chemokine can bind a

mammalian CCR5 receptor, and that Applicants have provided examples of how to determine if an antibody to a mammalian CCR5 inhibits binding of a chemokine to the CCR5 (see, for example, page 62, line 5 through page 63, line 7), the specification clearly provides enablement for antibodies which inhibit binding of a chemokine to a mammalian CCR5. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 75-82, 84-94, 96-106 and 108-110 Under 35 U.S.C. § 112, First Paragraph

Claims 75-82, 84-94, 96-106 and 108-110 are rejected by the Examiner under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. (Office Action, page 5, first paragraph).

Specifically, the Examiner states that "although three species of chemokines that bind CCR5 are disclosed, there does not appear to be an adequate written description of the genus because no structural basis is identified for their binding function, and because the genus of chemokines was well known in the art to be large, particularly when the chemokine can bind to any mammalian CCR5." (Office Action, page 5, third paragraph).

Applicants respectfully disagree. The claims do not encompass any chemokine. Only those chemokines that bind CCR5 are encompassed. Chemokines that bind CCR5 are known to one of ordinary skill in the art, examples of same are provided by Applicants, and the mere recitation of a CCR5-binding chemokine imparts sufficient description to one of ordinary skill in the art to appreciate which chemokines are envisaged by Applicants. In particular, the Specification at pages 1-3 indicates that it is known in the art that CCR5 is a receptor for the CC or β chemokines, the family of which shares a structural motif. "What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail." (MPEP, 8th ed., revision 1, § 2163). Thus, the genus of CCR5-binding chemokines has adequate written description given the level of skill in the art, and the number of representative species provided by Applicants. One of ordinary skill in the art would readily recognize that Applicants were in possession of the claimed invention at the time of filing of the application.

Furthermore, the Examiner has stated that "the specification does not provide sufficient written support for the genus of polypeptides that includes any "mammalian" CCR5 protein. Consequently, adequate written support is lacking for the broader genus of antibodies which bind any "mammalian" CCR5." (Office Action, page 5, fourth paragraph).

Applicants respectfully disagree. The term "mammalian CCR5" is sufficient description for one of ordinary skill in the art to appreciate what is encompassed by the invention. Furthermore, the specification as filed provides examples of mammalian CCR5, for example, human, non-human primate and murine CCR5 (see, for example, p. 12, lines 3-6). The written description requirement for a claimed genus is satisfied through sufficient description of a representative number of species, wherein a representative number is an inverse function of the skill and knowledge in the art. (MPEP, 8th ed., revision 1, § 2163). Thus, Applicants respectfully submit that the term "mammalian CCR5" is adequately supported in the specification, as filed. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 75-82, 84-94 and 96-98 Under 35 U.S.C. § 102(e)

Claims 75-82, 84-94 and 96-98 are rejected by the Examiner under 35 U.S.C. § 102(e) as being anticipated by Li *et al.* (U.S. Patent No. 6,025,154; IDS Ref. AE) *as evidenced by* Wu *et al.* (J. Exp. Med. 1997; 186(8):1373-1381; IDS Ref. AS4).

Specifically, the Examiner states that Li *et al.* teach an antibody to human HDGNR10, which is the same protein as human CCR5.

Applicants respectfully traverse this rejection. For anticipation under 35 U.S.C. § 102, the reference must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present (MPEP 8th ed., revision 1, § 706.02). For a reference to anticipate by inherency, it is required that "the prior art *necessarily* functions in accordance with, or includes, the claimed limitations." *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) (emphasis added). Furthermore, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Continental Can Co.USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991). Moreover, it is well settled that disclosure of a genus does not

necessarily anticipate a claim to a species within the genus. In order for a genus to anticipate a species, one of ordinary skill in the art must be able to "at once envisage" the species from the disclosure of the genus. *In re Petering*, 301 F2d 676, 133 U.S.P.Q. (C.C.P.A. 1962); *In re Meyer*, 599 F.2d 1026, 202 U.S.P.Q. 175 (C.C.P.A. 1979); *Akzo N. V. v. International Trade Comm'n*, 808 F.2d 1471, 1 U.S.P.Q.2d 1241 (Fed. Cir. 1986).

Li *et al.* does not explicitly teach or suggest every aspect of the invention of Claims 75-82, 84-94 and 96-98, nor do the antibodies disclosed by Li *et al. necessarily* include each and every aspect of the claimed invention. Li *et al.* merely provides a generic disclosure that antibodies to the newly cloned HDGNR10 (CCR5) can be made. This disclosure by Li *et al.* does not allow one of ordinary skill in the art to "at once envisage" an antibody which binds CCR5, inhibits binding of a chemokine to CCR5 and inhibits one or more functions associated with binding of the chemokine to the receptor as recited in Claims 75-82, 84-94 and 96-98. Thus, the disclosure of Li *et al.* does not anticipate the claimed invention.

Li *et al.* disclose the identification of human G-protein chemokine receptor CCR5 and the DNA encoding the receptor. Li *et al.* also state that the receptor can be used as an immunogen to generate antibodies to the receptor using methods known in the art. Li *et al.* does not produce any antibodies to the disclosed receptor, and Li *et al.* do not teach or suggest any antibody or antigen binding fragment which binds CCR5 and inhibits binding of a chemokine to CCR5, much less an antibody or antigen binding fragment which also inhibits one or more functions associated with binding of a chemokine to CCR5. Clearly the disclosure by Li *et al.* of the genus of antibodies which bind CCR5 encompasses a myriad of antibody species having very different physical composition (amino acid sequence, secondary and tertiary structure) and functional properties. From this generic disclosure one of ordinary skill in the art would not immediately envisage a species of antibody which binds CCR5, inhibits binding of a chemokine to the receptor and inhibits one or more functions associated with binding of the chemokine to the receptor. It clearly not true that antibodies which bind CCR5 *necessarily* inhibit binding of a chemokine to the receptor and *necessarily* inhibit one or more functions associated with binding of the chemokine to the receptor as recited in the instant claims. These properties cannot be said to be inherent in an antibody which binds CCR5.

In fact, in practice it proved to be very difficult to obtain an antibody with the properties recited in the instant claims. In the concurrently submitted copy of a Declaration of Walter Newman, Ph.D., Under 37 C.F.R. § 1.132, previously submitted in parent application no. 08/739,507, as Exhibit A, Dr. Newman states that approximately 17 different hybridoma fusions (from spleen cells obtained from mice immunized with CCR5-expressing transfectants) were screened, two of which produced antibodies reactive with CCR5 transfectants. One of these fusions provided approximately 25 CCR5-reactive supernatants, about one-half of which were followed up with subcloning and further analysis. One of these produced approximately two reactive supernatants, one of which produced antibody 2D7 described in the application. This antibody binds CCR5, inhibits binding of a chemokine to the receptor and inhibits one or more functions associated with binding of the chemokine to the receptor.

Further evidence of the difficulty in producing anti-CCR5 antibodies having the particular functional properties recited in the instant claims is provided by Olson *et al.* (*J. Virol. 73(5)*:4145-4155 (1999); IDS Ref. AW5). Olson *et al.* generated a number of anti-CCR5 murine monoclonal antibodies (PA8, PA9, PA10, PA11, PA12 and PA14), all of which were able to inhibit HIV-1 envelope-mediated membrane fusion; all of these antibodies blocked fusion between CD4+CCR5+ PM1 cells and HeLa- $Env_{JR\text{-}FL+}$ cells in a RET assay. However, of these antibodies, only PA14 blocked calcium mobilization induced by the chemokine RANTES.

The data and results provided above further demonstrate that one of ordinary skill in the art with the disclosure of Li *et al.* in hand would not have "at once envisaged" the particular species of antibody or antigen binding fragment recited in Claims 75-82, 84-94 and 96-98. One of ordinary skill in the art would have been faced with a broad spectrum of possible antibody species with different physical and functional properties, and there is no teaching or suggestion provided by Li *et al.* which would have directed one of ordinary skill in the art to the particular species recited in the instant claims. Li *et al.* merely disclose a new receptor and state that antibodies to the receptor can be made; this disclosure clearly does not anticipate an antibody or antigen binding fragment having the functional properties recited in Claims 75-82, 84-94 and 96-98.

The Examiner has cited Wu *et al.* (*J. Exp. Med. 186(8)*:1373-1381 (1997); IDS Ref. AS4) as a secondary reference, apparently to show that characteristics not disclosed in the primary

reference are inherent (MPEP, 8th ed., revision 1, § 2131.01). However, such a showing requires that the secondary reference "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill" (MPEP, 8th ed., revision 1, § 2131.01 III; citing *Continental Can Co. USA v. Monsanto Co.,* 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991)).

Wu *et al.* does not fulfill this requirement. The Examiner states that Wu *et al.* evidence that those antibodies which block binding of the chemokines MIP-1α, MIP-1β and RANTES to CCR5 bind the second extracellular loop of CCR5. This does not establish, however, that an antibody to CCR5 (as disclosed by Li *et al.*) would *necessarily* inhibit binding of a chemokine to CCR5 and *necessarily* inhibit one or more functions associated with binding of the chemokine to CCR5. Indeed, as discussed above, the premise that an antibody which binds CCR5 *necessarily* inhibits binding of a chemokine to the receptor and *necessarily* inhibits one or more functions associated with binding of the chemokine to the receptor is clearly false. It is indisputable that antibodies which bind CCR5 may not inhibit binding of chemokine and/or inhibit one or more functions association with binding of chemokine to receptor (see, for example, Olson *et al.*). Thus, the functional properties recited in the instant claims are not inherent properties of the antibody disclosed by Li *et al.*, and the reference does not explicitly or impliedly teach or suggest all elements of the claimed invention. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 75-82, 84-94 and 96-98 Under 35 U.S.C. §102(e)

Claims 75-82, 84-94 and 96-98 are rejected by the Examiner under 35 U.S.C. § 102(e) as being anticipated by Hoxie (U.S. Patent No. 5,994,515; IDS Ref. AB) *as evidenced by* Olson *et al.* (*J. Virol.* 1999; 73:4145-4155; IDS Ref. AW5) and Wu *et al.* (*J. Exp. Med.* 1997; 186(8):1373-1381; IDS Ref. AS4).

Specifically, the Examiner states that Hoxie teaches and claims an antibody to the HIV co-receptor human CCR5.

Applicants respectfully traverse this rejection. For anticipation under 35 U.S.C. §102, the reference must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present (MPEP, 8th ed., revision 1, § 706.02). For a

reference to anticipate by inherency, it is required that "the prior art *necessarily* functions in accordance with, or includes, the claimed limitations." *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) (emphasis added). Furthermore, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Continental Can Co.USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991). Hoxie does not explicitly teach or suggest every aspect of the invention of Claims 75-82, 84-94 and 96-98. Furthermore, Hoxie does not inherently teach each and every aspect of the claimed invention.

Hoxie teaches an "antiviral antibody" which binds to a cellular protein essential for entry of an immunodeficiency virus into a cell expressing that protein. The antibody disclosed by Hoxie is an "antiviral antibody" by virtue of its ability to inhibit entry of the immunodeficiency virus into a cell bearing the cellular protein by binding to the cellular protein (col. 6, lines 21-31). Hoxie states that the cellular protein can be, for example, CCR5. However, it is noteworthy that Hoxie does not actually disclose the production of an "antiviral" antibodies which bind to CCR5. In fact, the specific examples in Hoxie are directed solely to antibodies which bind to CXCR4 and which inhibit entry of the virus into the cell.

Claims 75-82, 84-94 and 96-98 of the subject application recite that the antibody or antigen binding fragment inhibits binding of a chemokine to the receptor, and inhibits one or more functions associated with binding of the chemokine to the receptor. This aspect of the invention is not taught or suggested by Hoxie, as Hoxie does not explicitly disclose an antibody or antigen binding fragment which binds CCR5, inhibits *chemokine* binding to CCR5 and inhibits one or more functions associated with chemokine binding to CCR5.

Moreover, Hoxie does not inherently disclose an antibody or antigen binding fragment which binds CCR5, inhibits *chemokine* binding to CCR5 and inhibits one or more functions associated with chemokine binding to CCR5. As shown by the references cited in the Supplemental Information Disclosure Statement submitted April 18, 2002, HIV viral co-receptor activity is dissociable from chemokine ligand-dependent signaling responses for CCR5. For example, Atchison *et al.* (*Science 274*:1924-1926 (1996); IDS Ref. AZ5) demonstrate that a chimera of the NH_2-terminus of human CCR5 fused to the remainder of human CCR2B retains vigorous function as a co-receptor for HIV-1 while exhibiting no detectable signaling response to

cognate ligands for CCR5 or CCR2B (page 1925, col. 3, lines 3-12). This data demonstrates that while the amino-terminal portion of CCR5 appears to be sufficient for CCR5 to function as a co-receptor for HIV, the amino terminal portion of CCR5 is not sufficient for chemokine response. Gosling *et al.* (*Proc. Natl. Acad. Sci. USA 94*:5061-5066 (1997); IDS Ref. AX5) disclose that chimeras of CCR5 that failed to signal in response to chemokines remained fully functional as co-receptors for HIV (page 5061, col. 1, lines 24-26).

These publications demonstrate that HIV binds to a particular portion of the CCR5 receptor (the amino-terminus), while chemokines bind to a distinct portion of the receptor. The ability of an anti-CCR5 antibody to inhibit HIV entry into a CCR5-bearing cell is not coextensive with the ability of an anti-CCR5 antibody to inhibit chemokine binding to CCR5. In fact, the Examiner acknowledges that HIV co-receptor function and functions associated with chemokine binding to CCR5 can be dissociated. Thus, it is clear that an anti-CCR5 antibody which inhibits HIV entry into a CCR5-bearing cell does not inherently possess the ability to inhibit chemokine binding to CCR5 and/or the ability to inhibit one or more functions associated with binding of the chemokine to the receptor. Accordingly, Hoxie does not explicitly or impliedly disclose an antibody or antigen binding fragment which binds CCR5, inhibits chemokine binding to CCR5 and inhibits one or more functions associated with chemokine binding to CCR5. Hoxie merely discloses one species of anti-CCR5 antibodies (which inhibits HIV entry into a CCR5-bearing cell), and this species does not anticipate the species of anti-CCR5 antibody recited in the subject application (which inhibits chemokine binding to CCR5 and inhibits one or more functions associated with binding of chemokine to receptor).

The Examiner cites two secondary references, Olson *et al.*, and Wu *et al.*, to show that characteristics that were not disclosed in Hoxie are inherent in the monoclonal antibodies of Hoxie. The Examiner states that Wu *et al.* evidence that those antibodies which block binding of the chemokines MIP-1α, MIP-1β and RANTES to CCR5 bind the second extracellular loop of CCR5. In addition the Examiner states that Olson *et al.* show that the antibodies most effective at inhibiting HIV membrane fusion and viral entry are the antibodies that also inhibit calcium flux, and thus that a screen for antibodies which inhibit HIV infection would necessarily identify antibodies that inhibited chemokine binding and one or more functions associated with chemokine binding. This assertion is not true however. The teaching that the antibodies most

effective at inhibiting HIV entry also inhibit chemokine binding does not mean that an antibody which inhibits HIV entry as disclosed by Hoxie would *necessarily* have the properties recited in the instant claims. An antibody which inhibits CCR5-mediated HIV entry into a cell is not *necessarily* an antibody which inhibits binding of a chemokine to CCR5 and inhibits one or more functions associated with binding of the chemokine to the receptor.

Thus, because Hoxie does not teach every aspect of the claimed invention either explicitly or impliedly, Hoxie does not anticipate the invention of Claims 75-82, 84-94 and 96-98. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 75-82, 84-94, 96-106 and 108-110 Under 35 U.S.C. §102(e)

Claims 75-82, 84-94, 96-106 and 108-110 are rejected by the Examiner under 35 U.S.C. § 102(e) as being anticipated by Littman *et al.* (U.S. Patent No. 5,939,320; IDS Ref. AA) *as evidenced by* Olson *et al.* (*J. Virol.* 1999; 73:4145-4155, IDS Ref. AW5) and Wu *et al.* (*J. Exp. Med.* 1997; 186(8):1373-1381; IDS Ref. AS4).

Applicants respectfully disagree. For anticipation under 35 U.S.C. § 102, the reference must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present (MPEP, 8th ed., revision 1, § 706.02). For a reference to anticipate by inherency, it is required that "the prior art *necessarily* functions in accordance with, or includes, the claimed limitations." *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999) (emphasis added). Furthermore, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Continental Can Co.USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991). Littman *et al.* does not teach or suggest every aspect of the invention of Claims 75-82, 84-94, 96-106 and 108-110, nor are each and every element of the claimed invention inherent in Littman *et al.*

Littman *et al.* teach the identification and application of an agent which is capable of promoting the translocation of M-tropic HIV through the membrane of a target CD4+ cell (e.g., CCR5), as well as agents (e.g., antibodies) which are able to inhibit this translocation. Littman *et al.* do not produce any such antibodies. Moreover, Littman *et al.* do not disclose any antibodies, much less anti-CCR5 antibodies, which inhibit binding of a chemokine to a chemokine receptor

and which inhibit one or more functions associated with binding of chemokine to receptor. Thus, Littman, *et al.* does not explicitly disclose an antibody or antigen binding fragment which binds CCR5, inhibits chemokine binding to CCR5 and inhibits one or more functions associated with chemokine binding to CCR5.

Furthermore, Littman *et al.* also does not impliedly disclose an antibody or antigen binding fragment which binds CCR5, inhibits chemokine binding to CCR5 and inhibits one or more functions associated with chemokine binding to CCR5. As discussed above with regard to the §102 rejection over Hoxie, the Examiner has acknowledged that HIV viral co-receptor activity is dissociable from chemokine ligand-dependent signaling responses for CCR5. It is clear that antibodies which can inhibit the entry of HIV into CCR5-bearing cells are not *necessarily* able to inhibit binding of a chemokine to CCR5 and/or inhibit one or more functions associated with binding of chemokine to CCR5. Littman *et al.* does not teach or suggest any antibodies which bind CCR5, inhibit binding of a chemokine to CCR5 and inhibit one or more functions associated with binding of a chemokine to CCR5 as recited in the instant claims; indeed, Littman *et al.* does not produce any anti-CCR5 antibodies which could even be assessed for such functions. Littman *et al.* merely states that its disclosure relates to an antibody which is able to inhibit entry of HIV into a cell bearing, e.g., CCR5. This disclosure does not explicitly or impliedly anticipate the invention of the subject claims, which recite an antibody which binds CCR5, inhibits binding of a chemokine to CCR5, and inhibits one or more functions associated with binding of chemokine to CCR5.

The Examiner also asserts that monoclonal antibodies which inhibit HIV infection and which inhibit chemokine binding to CCR5 and one or more functions associated with chemokine binding to CCR5 are produced upon immunization with CCR5 (Office Action, page 8, sixth paragraph). Once again, the possibility that such antibodies *may be* produced upon immunization with CCR5 does not satisfy the required showing that an anti-CCR5 antibody which inhibits HIV entry into a cell is *necessarily* an antibody which inhibits chemokine binding to CCR5 and inhibits one or more functions associated with said binding. Applicants submit that such a showing cannot be made. As with Hoxie above, Littman *et al.* merely disclose one species of anti-CCR5 antibody, and this species does not anticipate the species of antibody recited in the claims of the subject application.

In view of the discussion presented above, Applicants respectfully submit that the Examiner's rejection is not supported by the evidence and, thus, the cited art is not sufficient to anticipate the claimed invention. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 75-79, 84-85, 87-91, 96-97, 99-103 and 108-109 Under 35 U.S.C. §103(a)

Claims 75-79, 84-85, 87-91, 96-97, 99-103 and 108-109 are rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Chuntharapai *et al.* (U.S. Patent No. 5,543,503; IDS Ref. AD) in view of either Raport *et al.* (*J. Biol. Chem. 271*:17161-17166 (1996); IDS Ref. AW), Samson *et al.* (*Biochem. 35*:3362-3367 (1996); IDS Ref. AV), or Combadiere *et al.* (*J. Leukoc. Biol. 60*:147-152 (1996); IDS Ref. AT3), as evidenced by Wu *et al.* (*J. Exp. Med.* 1997; 186(8):1373-1381; IDS Ref. AS4).

Specifically, the Examiner states that Chuntharapai *et al.* teach the production of antibodies that can inhibit binding of the chemokine IL-8 to its receptor, and that this method can be applied to all members of the PF4A superfamily which includes the CXC chemokines and the CC chemokines. The Examiner states that each of Raport *et al.*, Samson *et al.* and Combadiere *et al.* teach CCR5. The Examiner concludes that Chuntharapai *et al.* provide a methodology for producing antibodies to CCR5 that block binding of chemokine ligands and therefore block their recruitment function. The Examiner concludes that the ordinary artisan at the time of the invention would have been motivated to produce such antibodies to CCR5 and would have had a reasonable expectation of success not only for producing antibodies to CCR5 in general but also for producing antibodies to CCR5 that block binding of the chemokine ligands MIP-1α, MIP-1β and RANTES and that inhibited their function.

In re Vaeck sets forth a two-prong standard for establishing combined reference obviousness; both prongs of the test must be met in order for such a rejection to be proper. *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Where the claimed invention is rejected as obvious in view of a combination of references, § 103 requires both (1) that "the prior art would have suggested to those of ordinary skill in the art that they should...carry out the claimed process"; and (2) that the prior art should establish a reasonable expectation of success. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Additionally, the cited references must teach or suggest

all of the claim limitations. "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *Id.* None of the combinations based on the cited references teaches or suggests the claimed invention. Moreover, no reasonable expectation of success founded in the prior art exists with respect to the claimed antibodies as discussed in detail below.

Chuntharapai *et al.* teach the production of anti-IL-8 receptor antibodies which inhibit binding of IL-8 to IL-8R. The teachings of Chuntharapai *et al.* are limited to the disclosure of an anti-IL-8R antibody which inhibits binding of IL-8 to IL-8R. Chuntharapai *et al.* does not teach or suggest that their anti-IL-8R antibody inhibits any function associated with binding of IL-8 to IL-8R. In fact, Chuntharapai *et al.* demonstrates only a binding assay because there is no good bioassay specific for IL-8R. Thus, it appears that the authors were able to test their anti-IL-8R antibody only for the ability to inhibit binding of IL-8 to IL-8R, and did not test for the ability to inhibit function associated with binding of IL-8 to IL-8R.

Raport *et al.* describe the identification and characterization of cDNA encoding CCR5 and disclose that the encoded receptor binds RANTES, MIP-1α and MIP-1β. Raport *et al.* do not teach or suggest antibodies to the CCR5 receptor, nor do they teach or suggest antibodies which can inhibit the binding of a chemokine to CCR5 and inhibit function associated with binding of chemokine to receptor.

Samson *et al.* teach the cloning of a human gene encoding chemokine receptor CCR5 and assess the physiological responses to various chemokines mediated by CCR5. The reference does not disclose any anti-CCR5 antibodies and does not teach or suggest the production of anti-CCR5 antibodies, including those which inhibit binding of a chemokine to CCR5 and inhibit one or more functions associated with binding of chemokine to receptor.

Combadiere *et al.* teach the cloning of a CCR5 variant whose amino acid sequence differs from the amino acid sequence of CCR5 disclosed by Samson *et al.* at amino acid 90. Once again, Combadiere *et al.* do not teach or suggest antibodies to CCR5 which inhibit binding of a chemokine to CCR5 and inhibit function associated with binding of chemokine to receptor.

Applicants respectfully submit that the combination of Chuntharapai *et al.* with Raport *et al.*, Samson *et al.* and Combadiere *et al.* does not teach or suggest all of the limitations of the instant claims as required for a proper rejection under 35 U.S.C. § 103 because even the

combination of references does not teach or suggest an anti-CCR5 antibody which inhibits binding of a chemokine to CCR5 and inhibits one or more functions associated with binding of the chemokine to the receptor. None of the cited references teaches or suggests any antibodies which are able to inhibit one or more functions associated with binding of a chemokine to its receptor, let alone anti-CCR5 antibodies which have the requisite functional properties.

Chuntharapai *et al.* merely discloses an anti-IL-8R antibody which inhibits binding of IL-8 to IL-8R but does not disclose the functional effect of this inhibition. The determination that an antibody is able to inhibit binding of IL-8 to IL-8R does not mean that antibody is able to inhibit one or more functions associated with binding of the chemokine (e.g., IL-8) to receptor (e.g., IL-8R). As disclosed in Olson *et al.* and in the Declaration, antibodies which inhibit binding of a chemokine may themselves trigger receptor function by virtue of their binding to the receptor (Olson *et al.*, page 4147, col. 2, lines 46-48; Declaration, paragraph 6). In this instance, inhibition of binding of the chemokine to the receptor would not inhibit the biological activities of the receptor which result from binding of the chemokine, as some or all of these activities can be potentiated by the antibody itself. The fact that an antibody which is capable of inhibiting binding of a chemokine to receptor can have several effects on the functions associated with binding of chemokine to receptor is evidenced by Frade *et al.* (*J. Immunol. 159*(11):5576-5584 (1997); IDS Ref. AY5). Frade *et al.* discloses the production of a panel of monoclonal antibodies capable of binding CCR2 as demonstrated by the fact that all six mAbs recognize THP-1 and Mono Mac 1 cells, as well as CCR2-transfected 293 cells, in flow cytometry analysis. However, an assessment of the functional effects of binding of these antibodies to the CCR2 receptor showed a widely varied functional response. Some antibodies had no effect on function in chemotaxis and calcium flux assays. Other antibodies (antagonists) inhibited one or the other of the assessed functions, while a third group of antibodies (agonists) caused an increase from baseline in one or more of the assessed functions. Thus, it is highly unpredictable from the mere disclosure of antibodies which inhibit the binding of chemokine (e.g., IL-8) to receptor (e.g., IL-8R) what the effect, if any, of such an antibody will be on functions associated with binding of the chemokine to receptor. Chuntharapai *et al.* cannot be fairly summarized as teaching an antibody which inhibits on or more functions associated with binding of a chemokine to its receptor, and the secondary references do not remedy this defect.

Thus, Applicants respectfully submit that the Examiner has not established a *prima facie* showing of obviousness under 35 U.S.C. § 103 because all of the claim limitations are not taught or suggested by the cited art.

Even assuming *arguendo* that the references were properly combined, whether or not the antibodies described by Chuntharapai *et al.* are capable of inhibiting chemokine binding to the IL-8 receptor, the teachings of the cited references do not establish a reasonable expectation of success in obtaining the anti-CCR5 antibodies with the requisite activity for a number of reasons.

First, CCR5 is distinct from IL-8 receptor. The prior art does not teach that CCR5 is equivalent to IL-8 receptor and in fact, CCR5 is not equivalent to the IL-8RA and IL-8RB receptors. Thus, there would be no reasonable expectation of success in making antibodies which both inhibit binding of chemokine to the CCR5 protein and inhibit one or more functions associated with binding of chemokine to CCR5 founded upon the teachings related to anti-IL-8RA/RB antibodies as disclosed by Chuntharapai *et al.*, since the prior art does not teach that CCR5 is equivalent to IL-8RA or IL-8RB, and because IL-8RA/RB and CCR5 are not in fact equivalents. CCR5 has a distinct primary amino acid sequence and a different structure and function from IL-8RA and IL-8RB. For example, studies with IL-8 receptors and antibodies thereto would have no bearing on the question of whether CCR5 chemokine binding regions might be immunogenic, and thus there would be no reasonable expectation of success in obtaining anti-CCR5 antibodies which inhibit chemokine binding.

As discussed in the copy of the concurrently submitted Declaration, it is very difficult to obtain antibodies to chemokine receptors such as CCR5. Moreover, the ability of an antibody to inhibit binding of a ligand to a receptor is dependent upon many factors. For example, one or more structural elements which are involved in ligand binding must be capable of inducing an immune response. The location of such epitopic regions within a protein is difficult to predict, and there is no reasonable expectation that the ligand binding regions of the receptor protein will be epitopic regions. Furthermore, even if the ligand binding regions are immunogenic, the resulting antibody may not interfere with the binding of a ligand to the receptor. For example, the portion of the receptor which binds to a ligand (e.g., a chemokine) may have a conformation which allows binding of both the ligand and antibody.

As discussed above, there is no reasonable expectation of success in producing antibodies to CCR5, and even if such an antibody is produced, there is no reasonable expectation that the antibody will inhibit binding of a ligand to the receptor. Moreover, as stated in the concurrently submitted copy of the Declaration, there is no reasonable expectation that the antibodies which are obtained will inhibit one or more functions associated with binding of the ligand to the receptor. Antibodies can function as agonists or antagonists of receptor function. That is, antibodies which bind to a particular receptor and inhibit binding of a ligand to the receptor can inhibit the function associated with the binding of the ligand to the receptor, or can induce or enhance the function associated with binding of the ligand to the receptor. Thus, antibodies which act as agonists of receptor function can "mimic" the effect of ligand binding and cause the same or increased downstream effects as binding of the ligand.

The concurrently filed copy of the Declaration provides additional evidence regarding the production of anti-CCR5 antibodies which supports the lack of a reasonable expectation of success in producing antibodies to CCR5 which inhibit binding of a ligand to the receptor and which inhibit one or more functions associated with binding of the ligand to the receptor. In the Declaration, Dr. Newman states that approximately 17 different hybridoma fusions were screened, two of which produced antibodies reactive with CCR5 transfectants. One of these fusions provided approximately 25 CCR5-reactive supernatants, about one-half of which were followed up with subcloning and further analysis. One of these produced approximately two reactive supernatants, one of which produced antibody 2D7 described in the application. Thus, prior to the present invention there was no reasonable expectation of success in producing antibodies which inhibit binding of a ligand to CCR5 and which inhibit one or more functions associated with binding of the ligand to the receptor, as such antibodies were very difficult to obtain.

Additionally, Olson *et al.* (*J. Virol. 73*(5):4145-4155 (1999); IDS Ref. AW5) generated a number of anti-CCR5 murine monoclonal antibodies (PA8, PA9, PA10, PA11, PA12 and PA14), all of which were able to inhibit HIV-1 envelope-mediated membrane fusion; all of these antibodies blocked fusion between CD4+ CCR5+ PM1 cells and HeLa- $Env_{JR\text{-}FL+}$ cells in a RET assay. However, of these antibodies, only PA14 blocked calcium mobilization induced by the

chemokine RANTES, and the calcium mobilization inhibiting activity of monoclonal antibody 2D7 was superior to that of PA14 (Figs. 3A and 3B of Olson *et al.*).

In view of the foregoing, it is clear that the requirements needed to establish the obviousness of the claimed invention in light of the cited references under *In re Vaeck* have not been met. For these reasons, Applicants respectfully submit that the combination of Chuntharapai *et al.*, Raport *et al.*, Samson *et al.* and Combadiere *et al.* does not render the subject invention obvious because the cited references, alone or in combination, do not teach or suggest all elements of the claimed invention and do not provide the ordinarily skilled artisan with a reasonable expectation of success in producing the claimed invention.

Furthermore, the Examiner's reliance on Wu *et al.* as evidence to support the obviousness rejection has apparently been based on improper hindsight reasoning, which is impermissible (MPEP, 8th ed., revision 1, § 2142). Thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 80-82, 86, 92-94, 98, 104-106 and 110 Under 35 U.S.C. §103(a)

Claims 80-82, 86, 92-94, 98, 104-106 and 110 are rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Chuntharapai *et al.* (U.S. Patent No. 5,543,503; IDS Ref. AD) in view of either Raport *et al.* (*J. Biol. Chem. 271*:17161-17166 (1996); IDS Ref. AW), Samson *et al.* (*Biochem. 35*:3362-3367 (1996); IDS Ref. AV), or Combadiere *et al.* (*J. Leukoc. Biol. 60*:147-152 (1996); IDS Ref. AT3), as evidenced by Wu *et al.* (*J. Exp. Med.* 1997; 186(8):1373-1381; IDS Ref. AS4), as applied to claims 75-79, 84-85, 87-91, 96-97, 99-103 and 108-109 above; and further in view of Ramakrishnan *et al.* (U.S. Patent No. 5,817,310).

Chuntharapai *et al.*, Raport *et al.*, Samson *et al.*, Combadiere *et al.*, and Wu *et al.*, have been discussed *supra*.

Ramakrishnan *et al.* disclose immunoglobulins (antibodies) and fragments thereof that bind to PDGF beta receptor (see, for example, Abstract and columns 8-9). Ramakrishnan *et al.* do not teach or suggest single chain, Fab, $F(ab')_2$ or chimeric antibodies that bind to a mammalian CCR5, and which inhibits binding of a chemokine to the receptor and inhibits one or more functions associated with binding of the chemokine to the receptor. The disclosure of antibody fragments and chimeric antibodies which specifically bind to a human type beta PDGF

receptor does not render obvious antibody fragments or chimeric antibodies which specifically bind a different receptor, and inhibit ligand binding to that receptor, and inhibit one or more functions associated with binding of the ligand to that receptor.

As discussed *supra*, Chuntharapai *et al.* with Raport *et al.*, Samson *et al.*, or Combadiere *et al.* and as evidenced by Wu *et al.*, do not teach or suggest all of the limitations of the instant claims. The teachings of Ramakrishnan *et al.*, fail to remedy these deficiencies. Thus, Ramakrishnan *et al.*, either alone or in combination with the other cited references, do not render the presently claimed invention obvious. Reconsideration and withdrawal of the rejections are respectfully requested.

Double Patenting Rejection

Claims 75-110 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over allowed claims 1-36 of copending Application No. USSN 08/893,911, now allowed.

Applicants will file as Terminal Disclaimer to overcome the Examiner's provisional obviousness-type double patenting rejection as appropriate upon notice of otherwise allowable subject matter in the present application. This will permit Applicants to assess the rejection in view of the claims as ultimately indicated to be allowable, since it is possible that the claims may change during the course of prosecution.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Lisa M. Treannie

Lisa M. Treannie
Registration No. 41,368
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: 4/11/03

MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the Title at page 1, line 1 with the below title marked up by way of bracketing and underlining to show the changes relative to the previous version of the title:

ANTI-CCR5 ANTIBODIES AND [METHODS OF USE THEREFOR] KITS COMPRISING SAME

Replace the paragraph at page 1, lines 3-7 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph:

This application is a continuation-in-part application of [copending] U.S. application Serial No. 08/893,911, filed July 11, 1997 (now issued as U.S. Patent 6,528,625), which is a continuation-in-part application of U.S. application Serial No. 08/739,507, filed October 28, 1996 (now abandoned). The teachings of these prior applications are incorporated herein by reference in their entirety.

Please also replace the title on the Abstract page, at page 80, line 1, with the following title marked up by way of bracketing and underlining to show the changes relative to the previous version of the title:

ANTI-CCR5 ANTIBODIES AND [METHODS OF USE THEREFOR] KITS COMPRISING SAME